Ultrastructural Studies in Hypertension

IV. Toxemia of Pregnancy

Edwin R. Fisher, M.D., V. Pardo, M.D., Ronald Paul, M.D., and T. T. Hayashi, M.D.

THE TERM TOXEMIA OF PREGNANCY refers to a variety of disorders including preeclampsia, eclampsia, and hypertensive vascular and renal disease complicating pregnancy. Clinical distinction of these entities is acceptably difficult if not inexact. Histologic study of percutaneous renal biopsy specimens from patients with toxemia has helped in the delineation of these disorders.[1] The results of early electron microscopic studies of such samples prompted investigators to ascribe a unique and characteristic lesion for preeclampsia and eclampsia characterized by swelling and vacuolation of glomerular endothelium, which has been designated as endotheliosis.[2] This demonstration of a pathognomonic lesion in toxemia was regarded to represent " . . . a major advance in our knowledge of this disease and especially in our ability to differentiate true toxemia from other hypertensive disease." [3] Subsequent studies confirmed the presence of glomerular endotheliosis in preeclampsia but also implicated other glomerular alterations as participating in its renal defect.[4-10] An increase in mesangial components was emphasized by Pirani *et al.*[4] as well as Ishikawa,[10] the latter regarding the endothelial changes secondary to mesangial involvement. Pirani *et al.*,[4] Mautner *et al.*,[5] and Hopper *et al.*[7] also called attention to the deposition of electron-dense material, which they considered analagous to the fibrinoid material detected by light microscopy within the mesangium and between the lamina densa and glomerular endothelium. The incidence of such deposits, as well as alterations of glomerular epithelium and interpretations concerning their significance, have varied.

The accumulation of information and experience derived from subsequent electron microscopic studies of a variety of renal disorders has provoked us to re-evaluate the specificity of the ultrastructural renal

From the Departments of Pathology, and of Obstetrics and Gynecology, University of Pittsburgh School of Medicine, Veterans Administration Hospital, and Magee-Womens Hospital, Pittsburgh, Pa.

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Address for reprint requests: Dr. Edwin R. Fisher, Chief, Laboratory Service, Veterans Administration Hospital, University Drive, Pittsburgh, Pa. 15240.

changes encountered in a large number of patients with toxemia of pregnancy. Faith and Trump [9] recently have called attention to ultrastructural differences occurring in systemic lupus erythematosus, acute glomerulonephritis, and preeclampsia-eclampsia. Yet, they do suggest a unifying hypothesis for the pathogenesis and overlapping of the morphologic alterations. In some instances, the changes appear to be quantitative rather than qualitative.

Materials and Methods

Intravitam percutaneous renal biopsies were performed with a Menghini needle on 51 hypertensive pregnant women. Eight were clinically considered as exhibiting moderate preeclampsia (Table 1). Criteria for this diagnosis included consistent blood pressure determinations of 140/90 mm. Hg during the last trimester of pregnancy or a rise in blood pressure during this period (30 mm. Hg systolic and 15 mm. Hg diastolic). Proteinuria exceeding 0.5 gm./24 hr. was observed in all but 2 of the patients with preeclampsia. Edema was variable. Eleven patients were classified as severe preeclamptics (Table 1). Elevation of blood pressure occurred within the last trimester of pregnancy and was 160/110 mm. Hg or greater. Proteinuria exceeding 5 gm./day and oliguria (400 ml. or less per day) were present consistently. Eight patients were considered to have essential hypertension (Table 2) because of elevation of blood pressure throughout the gestational period. Many of these had a previous or family history of hypertension. A clinical diagnosis of preeclampsia superimposed upon essential hypertension was made on 8 patients (Table 2). Such patients, although hypertensive during the early periods of pregnancy, exhibited further rise in blood pressure of at least 30 mm. Hg systolic and 15 mm. Hg diastolic during the last trimester of pregnancy. Proteinuria was noted in 4. A diagnosis of unrelated or primary renal disease was considered in 6 patients (Table 3). Blood pressure elevation was recognized during the early phase of pregnancy and was associated with massive proteinuria. BUN and serum creatinine levels were elevated in many. Ten patients were regarded as exhibiting unclassified toxemia of pregnancy (Table 3). Although elevation of blood pressure occurred usually during the second half of gestation, the hypertension was not consistent. No previous or familial history of hypertension could be elicited, and proteinuria was not encountered.

Three patients with severe preeclampsia, and each with a diagnosis of essential hypertension or primary renal disease, exhibited convulsions during the course of their illness.

All biopsies were performed within 72 hr. following delivery. Tissue was minced immediately and fixed in 1% osmium tetroxide buffered with veronal acetate pH 7.4 or, as in Patients 1, 2, and 11 (Table 1), was longitudinally bissected. One portion of the latter was minced and fixed in osmium tetroxide as above, and the other frozen on Dry Ice. Osmium-fixed tissue was dehydrated and embedded in Maraglas. Ultrathin sections were stained with lead citrate and examined with a Philips EM 200 electron microscope. At least three glomeruli from each patient were available for study. All specimens were examined without prior knowledge of the clinical diagnosis. The degree of endothelial hypertrophy and mesangial thickening was subjectively graded 1–3+. An index of severity was determined for each group by dividing the total of degrees of individual change by the total number of patients in the group. In addition, patients without recognizable renal alteration were classified as 0; those in whom only one alteration—i.e., either endotheliosis,

Table 1. Clinical and Ultrastructural Features of Patients Clinically Diagnosed as Having Severe and Moderate Preeclampsia

Pt.	Age	Gravida	Blood pressure (mm.Hg)		Serum levels (mg./100 ml.)			Urinary protein (gm./24 hr.)	E. M. changes			
			At biopsy	During illness	BUN	Creatinine	Uric acid		Endotheliosis	Mesang. thick.	Deposits	Class
Severe Preeclampsia												
1	17	1	146/84	180/140	10	1.4	10.7	5.2	+	3+	+	III
2*	23	1	128/90	210/120	20	1.4	5.9	1.5	2+	0	+	II
3	19	1	152/110	180/110	26	1.3	10.4	1.0	3+	3+	+	III
4*	20	1	120/84	210/110	19	1.1	8.5	3.4	3+	0	+	II
5	18	1	150/110	210/140	35	1.3	12.0	1.1	2+	2+	0	II
6	18	1	120/90	210/110	38	1.3	12.6	4.5	3+	0	0	I
7*	16	1	144/80	160/110	18	1.2	10.6	12.0	3+	+	+	III
8	21	1	140/90	170/110	15	1.1	9.1	2.8	0	2+	+	II
9	19	1	128/100	160/120	23	1.3	8.6	0.6	3+	3+	+	III
10	16	1	135/85	150/110	8	1.2	8.0	0.2	3+	2+	0	II
11	21	1	158/90	190/130	12	1.1	5.6	1.3	3+	2+	+	III
Index of severity									2.4	1.6		
Moderate Preeclampsia												
12	18	1	120/70	160/110	11	—	10.2	0.86	3+	0	+	II
13	19	1	130/90	170/120	14	—	7.1	1.80	2+	+	+	III
14	21	1	136/90	180/130	12	1.1	5.6	1.30	3+	0	+	II
15	16	1	140/90	170/90	13	—	5.0	5.20	3+	0	0	I
16	16	1	142/94	170/110	7	1.1	8.1	0.20	+	3+	+	III
17	17	1	136/90	150/110	12	0.9	7.1	2.70	3+	3+	+	III
18	19	1	110/60	155/105	19	0.8	7.1	0.60	0	2+	0	I
19	20	1	144/100	150/120	28	0.9	10.8	0.30	0	0	0	0
Index of severity									1.9	1.1		

* Convulsions.

Table 2. Clinical and Ultrastructural Features of Patients Clinically Diagnosed as Having Essential Hypertension With and Without Preeclampsia

Pt.	Age	Gravida	Blood pressure (mm.Hg)		Serum levels (mg./100 ml.)			Urinary protein (gm./24 hr.)	E. M. changes				
			At biopsy	During illness	BUN	Creatinine	Uric acid		Endotheliosis	Mesang. thick.	Deposits	Art. hyal.*	Class
						With Preeclampsia							
20	35	6	176/100	200/120	8	0.9	5.9	1.70	0	3+	0	+	I
21	37	3	140/90	160/110	32	1.2	7.2	0.17	2+	3+	0		II
22	33†	2	170/110	200/100	28	1.2	7.5	1.20	3+	+	+	+	III
23	30	2	142/100	180/110	11	0.8	7.7	0.44	0	0	+		I
24	29	4	155/100	165/105	9	1.1	6.3	3.60	3+	+	+		III
25	32	5	130/90	190/110	10	0.7	5.2	0.70	0	2+	+		II
26	30	5	130/80	170/110	26	0.8	10.7	1.50	+	2+	+	+	III
27	27	4	130/84	180/130	11	0.8	8.6	0.28	0	0	0		0
Index of severity									1.1	1.5			
						Without Preeclampsia							
28	21	3	158/100	160/112	7	0.7	3.3	0.90	0	0	0	+	0
29	26	8	148/95	160/100	—	0.9	4.0	0.04	2+	0	0		II
30	30	2	140/90	200/110	—	0.9	4.0	0.17	2+	3+	0		II
31	22	2	140/92	150/100	9	—	4.1	0.55	3+	3+	0		II
32	30	6	140/90	195/95	9	1.0	6.0	0.10	+	+	0	+	II
33	32	5	120/75	140/100	5	0.8	4.0	0.30	+	2+	0		II
34	35	2	140/92	190/130	—	—	5.7	0.48	2+	+	0		II
35	35	8	150/100	170/110	11	0.7	5.5	0	+	2+	0	+	II
Index of severity									1.5	1.5			

* Arteriolar hyalinosis.
† Convulsions.

Table 3. Clinical and Ultrastructural Features of Patients Clinically Diagnosed as Having Primary Renal Disease or Unclassified Toxemia

Pt.	Age	Gravida	Blood pressure (mm.Hg)		Serum levels (mg./100 ml.)			Urinary protein (gm./24 hr.)	E. M. changes			
			At biopsy	During illness	BUN	Creatinine	Uric acid		Endothe-liosis	Mesang. thick.	Deposits	Class
Primary Renal Disease												
36	23	1	112/88	160/100	36	1.3	6.6	15.0	3+	3+	+	III
37	17	1	128/80	140/110	23	0.9	10.8	1.5	2+	3+	+	III
38*	24	1	152/94	200/130	99	3.9	11.3	2.5	+	3+	0	II
39	17	1	124/92	160/110	37	1.6	10.0	5.2	+	2+	+	III
40	22	3	130/100	150/100	12	0.8	8.2	9.0	0	0	0	0
41	26	4	172/110	180/110	23	1.8	13.5	9.1	0	0	+	I
Index of severity									1.1	1.8		
Unclassified Toxemia												
42	18	1	138/90	148/100	10	—	5.4	0.20	0	0	+	I
43	16	1	110/70	150/100	—	—	4.8	0.22	0	0	0	0
44	20	1	150/90	170/120	10	0.8	6.5	0.20	0	0	0	0
45	15	1	120/80	150/100	9	0.8	5.6	0.03	+	0	0	I
46	16	1	118/70	133/100	8	—	6.2	0.40	0	0	0	0
47	19	1	120/72	180/100	11	1.0	5.8	0.10	0	3+	+	II
48	17	1	122/76	150/110	8	—	—	0.20	2+	2+	0	II
49	15	1	110/80	145/90	12	1.1	5.2	0.10	0	0	0	0
50	16	1	128/80	140/90	7	—	7.4	0.20	0	3+	0	I
51	19	1	112/80	150/95	18	—	7.6	0.28	2+	+	0	I
Index of severity									0.5	0.9		

* Convulsions.

mesangial thickening, or glomerular deposits—was present were categorized as Class I; those with two of these changes as Class II, and those in whom all were present were regarded as Class III.

Quick-frozen tissue was sectioned in a cryostat at −20° C., stained with anti-human γ- and β_{1c}-globulins, conjugated with fluorescein isothiocyanate, and examined by fluorescence microscopy.

Results

All patients with severe preeclampsia exhibited some renal alteration (Table 1). The most consistent change was swelling of glomerular endothelial cytoplasm resulting in narrowing of capillary lumens (Fig. 1 and 2). The latter were devoid of erythrocytes. Aggregates of platelets were noted within the lumen in one instance (Patient 5). The cytoplasm contained variably sized vacuoles. Numbers of mitochondria and elements of the coarse endoplasmic reticulum were variable in these cells. Occasional lipid droplets and cytosomes were also present. The plasma membrane, particularly that portion adjacent to the lamina densa, often exhibited small folds with resultant recesses and vesicle formation. Fenestrae between endothelial cells were inconspicuous in severely affected areas. The mesangium was generally thickened due to increase in lamina densa-like material and cellular hypertrophy (Fig. 3). The lamina densa was unaltered. In some instances, electron-dense deposits comprised of granules measuring 35–50 Å, and less frequent granular tetrads measuring 100 Å (ferritin) were noted between the lamina densa and endothelium, lamina densa proper, and lamina densa-like material comprising the mesangium. Rarely, this material was noted within endothelial cytoplasm (Fig. 1 and 2). The deposits were round to ovoid, and when found between the endothelium and lamina densa they often assumed a scalloped configuration (Fig. 4). In two instances (Patients 6 and 11) aggregates of dense homogeneous droplets (lipid ?) were noted within the lamina densa and between this structure and endothelium (Fig. 5). The mesangium was thickened due to an increase in lamina densa-like material and increased numbers of cellular elements. Glomerular epithelium was less frequently altered, but in those instances in which massive proteinuria was encountered foot processes of these cells were attenuated and their cytoplasm vacuolated (Fig. 6). In such instances, villous transformation of cell membranes frequently was noted. Epithelial cytoplasm occasionally contained cytosomes.

Portions of proximal and distal convoluted tubules generally were unaltered except for the presence of variable numbers of cytosomes similar to those noted in glomerular epithelium. Portions of collecting ducts and loops of Henle, available for study in three biopsy specimens, did not appear altered.

Some of these glomerular and tubular changes were recognized in all but one member of the groups designated as preeclampsia, essential hypertension with and without superimposed preeclampsia, and primary renal disease (Tables 1–3). Platelet aggregates were noted in capillary lumens in 2 patients with uncomplicated essential hypertension (Patients 21 and 26). Aggregates of the coarse, round bodies between endothelium and lamina densa were also noted in patients with essential hypertension, superimposed preeclampsia (Patient 23), and in one each with unclassified toxemia (Patient 47) and primary renal disease (Patient 39). Only 50% of patients with unclassified toxemia exhibited some glomerular alteration. The incidence of either endothelial and mesangial alterations and electron-dense extracellular glomerular deposits alone or together (Classes I, II, and III) was similar in all groups, except for that considered as unclassified toxemia in which instance no Class III lesions were noted (Fig. 7).

Although endotheliosis was encountered in biopsy specimens from patients in all groups, it was most frequent and severe (index of severity) in those considered to have moderate and severe preeclampsia, and least severe in those with unclassified toxemia. Mesangial change was also most severe in those with severe preeclampsia, although the difference noted between this group and the other groups was slight, excluding those with unclassified toxemia in which such alteration was mild. Deposits were noted in approximately 66% of patients with preeclampsia, primary renal disease, and essential hypertension with superimposed toxemia. On the other hand, only 20% of those with unclassified toxemia exhibited such lesions.

No striking difference in incidence or severity of glomerular lesions was encountered in the 5 patients who experienced convulsions and those in whom such episodes were not observed.

Except for the occurrence of the most severe glomerular epithelial changes in patients with the most marked proteinuria, no relationship between other glomerular alterations and any clinical or laboratory feature could be detected.

Arteriolar hyalinosis was encountered in six biopsy specimens, all from patients with essential hypertension with or without superimposed preeclampsia. The lesion was characterized by deposits of granules beneath the endothelium and occasionally within the wall of affected vessels. The fine structure of the granular material was indistinguishable from that noted in the more common extracellular glomerular deposits.

Juxtaglomerular cells were available for evaluation in 8 of the specimens from patients with preeclampsia, 6 in those with essential hyper-

tension with or without superimposed preeclampsia, and 3 each in patients with unclassified toxemia and primary renal disease. The juxtaglomerular cells were replete with true secretory granules (Fig. 8 and 9) in 4 of the patients with preeclampsia and 1 with preeclampsia superimposed upon essential hypertension. Some of these assumed paracrystalline configuration. In the other patients the juxtaglomerular cells contained lipofuscin bodies and only a rare true secretory granule.

Immunofluorescence studies revealed focal localization of γ-globulin within the basement membrane of two of the cases studied by this technique, but β_{1c} globulin was not found.

Discussion

It is appreciated that the findings in this study may not reflect the true incidence or severity of glomerular lesions in the patients with toxemia of pregnancy, since the biopsies were not performed during the height of the patient's illness but during the immediate postpartum period. At that time, the marked hypertension in all instances had abated, and many patients were normotensive. It is of interest that no correlation between the persistence of hypertension and incidence or severity of glomerular alterations was evident. The selection of the immediate postpartum period for biopsy was prompted by the risk attendant with the procedure during gestation, as well as information derived from previous, albeit limited, studies which revealed comparable endothelial and mesangial alterations in biopsy specimens from preeclamptic patients obtained during pregnancy and for as long as 2 weeks after delivery.[5,7] Indeed, Pirani *et al.*[4] considered some lesions to be more severe in the postpartum period. There is no unanimity of opinion as to whether the lesions observed in preeclamptic patients ever totally resolve. Complete resolution has been claimed by some [2] as early as 4 weeks postpartum, whereas others have noted their persistence—for as long as 2 years in some instances.[5]

The ultrastructural glomerular changes encountered in biopsy specimens from patients regarded as exhibiting moderate or severe preeclampsia were generally similar to those described previously by others.[2,4-10] However, we did not encounter extracellular deposits as frequently as noted by Faith and Trump.[9] It is possible that this discrepancy is related to differences in the time of biopsy performance. If this assumption is correct, it might indicate that such material is resolved quickly in the glomeruli of preeclamptics, a suggestion also made by Mautner *et al.*[5] Qualitatively, the extracellular deposits also were unlike those described by Faith and Trump.[9] The latter authors considered the material to be

flocculent and fibrillar, which allowed for the deposits' distinction from similar glomerular deposits in acute glomerulonephritis and lupus erythematosus. On the other hand, we have been impressed with their ultrastructural similarity to the deposits encountered in patients with these latter diseases, which we have had the opportunity to examine.[11] In addition, they appear qualitatively indistinguishable from glomerular deposits encountered in so-called idiopathic membranous glomerulonephritis with or without renal vein thrombosis,[12] and in cirrhotic (hepatic) lobular glomerulonephritis,[13] as well as the material comprising arteriolar hyalinosis noted in renal arterioles in patients with essential or renal hypertension,[14] adolescent diabetes mellitus,[15] gout,[16] progressive systemic sclerosis,[17] and many apparently normal persons of middle or later age.[14] Although there is some evidence relating these granular aggregates to antigen-antibody complexes in some experimental [18,19] and human diseases,[20-22] the results of our limited immunofluorescence studies of the preeclamptic kidneys in this study, as well as those of Vassalli, Morris, and McCluskey,[23] indicate that the lesions in preeclampsia are not immunologic by nature. The recognition of ferritin particles within these deposits does implicate their hematogenous derivation, but their precise pathogenesis remains unclear. Evidence obtained in this study revealing various stages of incorporation of this material into endothelial cells further supports this view as to such an origin and, in this regard, appears analagous to its presence within endothelial cells observed in some instances of arteriolar hyalinosis.[17] Some authors have regarded these extracellular deposits to represent the ultrastructural appearance of fibrinoid noted by light microscopy.[4,7] It is of interest that our experience in this situation is comparable to that noted previously in renal arterioles from patients with malignant hypertension in which no significant structural difference between hyalinosis and fibrinoid change, as revealed by light microscopy, could be detected—suggesting that these alterations represent a spectrum of the same pathologic process.[14] We are uncertain as to the significance of the aggregates of lipid-like droplets observed within the lamina densa in some patients designated as preeclamptic and in those groups which, in retrospect, might also be included as examples of this form of toxemia. Yet, the diagnostic significance of this feature is minimized when it is recognized that similar material has been noted in the renal lesion of cirrhotics exhibiting renal failure.[13]

The changes in glomerular epithelium and mesangium also do not appear unique for kidneys from patients with preeclampsia, the former having been described in a number of experimental as well as human renal diseases characterized by proteinuria. The severity of epithelial

changes in this study appeared related to the degree of proteinuria experienced by these patients, which is in accord with the findings of others,[7] as well as the view proposing that such alteration represents a consequence, rather than cause of, the proteinuria.[24]

Although it has been claimed that glomerular endotheliosis is pathognomonic for preeclampsia, the results of this as well as other pertinent studies challenge this conclusion. Unquestionably, endotheliosis and mesangial change were generally more severe in patients with preeclampsia. Yet, qualitatively, and occasionally quantitatively, similar alterations were encountered in glomeruli of some patients with essential hypertension. The subsequent clinical courses exhibited by both groups of patients and the presence of arteriolar hyalinosis only in those considered to represent examples of essential hypertension indicate that the clinical impressions in these instances were correct. The inconsistency of extracellular glomerular deposits in the kidney biopsy specimens from patients with preeclampsia limits their diagnostic value. Further, it is conceivable that these deposits might be encountered in kidneys from patients with essential malignant hypertension, since glomerular fibrinoid change represents one of its notable pathologic features. We,[11] as well as others,[9] have noted endothelial hypertrophy to be indistinguishable from that encountered in the kidneys from preeclamptic patients, in persons with lupus erythematosus (L.E.), and those with acute glomerulonephritis. Also, intramembranous (as well as extramembranous) localization of deposits occurs in membranous nephropathy[25] (idiopathic membranous glomerulonephritis)[12] and, as a result, may make it difficult to distinguish this primary renal disorder from the lesions noted in preeclampsia.

It is of interest in this regard that none of the biopsy specimens from patients in whom a clinical diagnosis of primary renal disease was entertained exhibited glomerular alterations which were unique nor could they be distinguished from those of patients considered to have preeclampsia. L.E. cell preparations performed on several of these were negative, and the subsequent clinical course of the patients in this group tends to discount a diagnosis of primary renal disease. This information indicates, contrary to the opinion of others,[26] that many women suspected of having primary renal disease during pregnancy may be experiencing preeclampsia. It is evident that such a conclusion is based largely upon exclusion and retrospective clinicopathologic correlation rather than unequivocal pathologic findings. Quantitation of the ultrastructural alterations noted in patients with preeclampsia appears limited in predicting the clinical severity of this disease, since no consistent correlation between clinical features, including the occurrence of con-

vulsions (eclampsia), and degree of glomerular alterations were observed. On the other hand, good correlation was observed between those individuals with mild disease who were designated as having unclassified toxemia. Members of the latter group revealed a paucity of ultrastructural glomerular changes. At present, it is highly suspect that these women may have had a very mild form of preeclampsia.

The pathogenesis of preeclampsia, as well as the glomerular alterations encountered in many of the patients with this disorder, remains an enigma. Glomerular endothelial reaction is well recognized as occurring in kidneys subjected to ischemia as is evident in nephrosclerosis. Renal plasma flow has been observed by several investigators [27,28] to be decreased in this form of toxemia. However, it is uncertain whether this alteration and the decreased glomerular filtration rate [28-30] are causally related to the endothelial reaction or result from it. The similarity in appearance of juxtaglomerular cell granules in several examples of preeclampsia in which such structures were available for study to those noted in kidneys from patients with renovascular hypertension [14] might be considered as evidence in support of the former possibility. Since the subsequent clinical course of such patients militates against the possibility that organic obstructive renovascular disease was present in these instances, the possibility is appealing that the hypertension, as well as glomerular alterations, result from a functional disorder of renal vasculature. In this regard, it is of interest to note that vasospasm of retinal arteries has been considered to represent a consistent and helpful diagnostic feature of this form of toxemia.[1,31] Furthermore, a clinical and pathologic syndrome simulating preeclampsia may be induced experimentally by the administration of desoxycorticosterone, salt, and renin.[32] There is considerable evidence identifying the juxtaglomerular cells as the renal source of this latter. Although some [23,33] have considered preeclampsia as possibly representing a manifestation of so-called intravascular coagulation, we could find no positive evidence to support this view. Platelet aggregates were noted in glomeruli from patients with essential hypertension as well as preeclampsia, and fibrin could not, at least in its classic form, be identified in the lesion. Whether the latter is due to the time of biopsy performance or other factors cannot be stated. However, it is conceivable that glomerular capillary thromboses observed by others could be the result, rather than the cause of, altered glomerular flow subsequent to vasospasm of the renal vasculature.

Summary

Percutaneous renal biopsy specimens obtained within 3 days after delivery from 51 women with hypertension during gestation were studied

by electron microscopy. Although glomerular endotheliosis and mesangial thickening were generally most severe in the group considered to exhibit moderate and severe preeclampsia, qualitatively, and occasionally quantitatively, similar lesions were noted in specimens from those patients regarded as having essential hypertension, primary renal disease, or unclassified toxemia. Arteriolar hyalinosis was observed only in the former. Extracellular glomerular deposits were as frequent in patients with clinical evidence of preeclampsia superimposed upon essential hypertension as in those with uncomplicated preeclampsia, but less in those with unclassified toxemia or in those who were considered clinically to have primary renal disease. The nature of these deposits is obscure, although results of immunofluorescence studies on a few samples, as well as their ultrastructural characteristics, minimizes the possibilities that they are immunologic in nature or related to a coagulation defect. This information and the similarity of the spectrum of ultrastructural changes encountered in patients with preeclampsia to that observed in other primary renal diseases minimizes their diagnostic specificity. Furthermore, no consistent correlation could be discerned between the severity of changes in individual members of the group with severe preeclampsia and their clinical course, including the occurrence of convulsive episodes. Retrospective analysis suggests that most patients considered to have primary renal disease or unclassified toxemia experienced mild or moderate preeclampsia.

The presence of abundant true secretory granules, as well as paracrystalline forms, in juxtaglomerular cells of many specimens from patients with preeclampsia suggests a vasospastic renovascular origin for the hypertension noted in these women.

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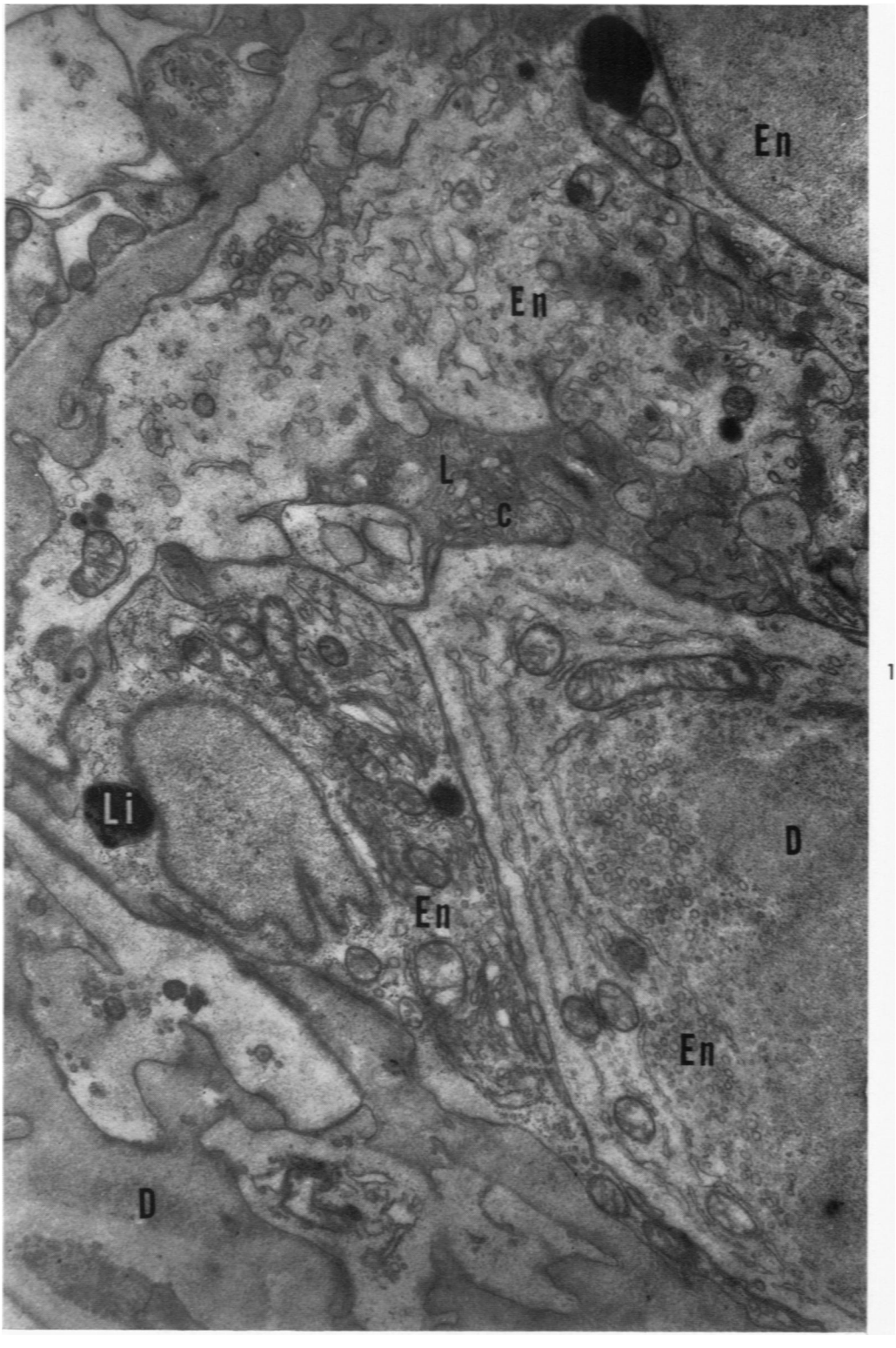
Legends for Figures

Fig. 1. Portion of glomerular capillary near mesangium from patient with preeclampsia. Lumen *(L)* is obliterated almost completely by enlarged endothelial cells *(En)*. Lipofuscin *(Li)* bodies, numerous vesicles, and vacuoles are noted in the cytoplasm. Dense granular material *(D)* is present in one cell and in lamina densa. Numerous cytofolds *(C)* of endothelial cells are evident. × 16,500.


En
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L
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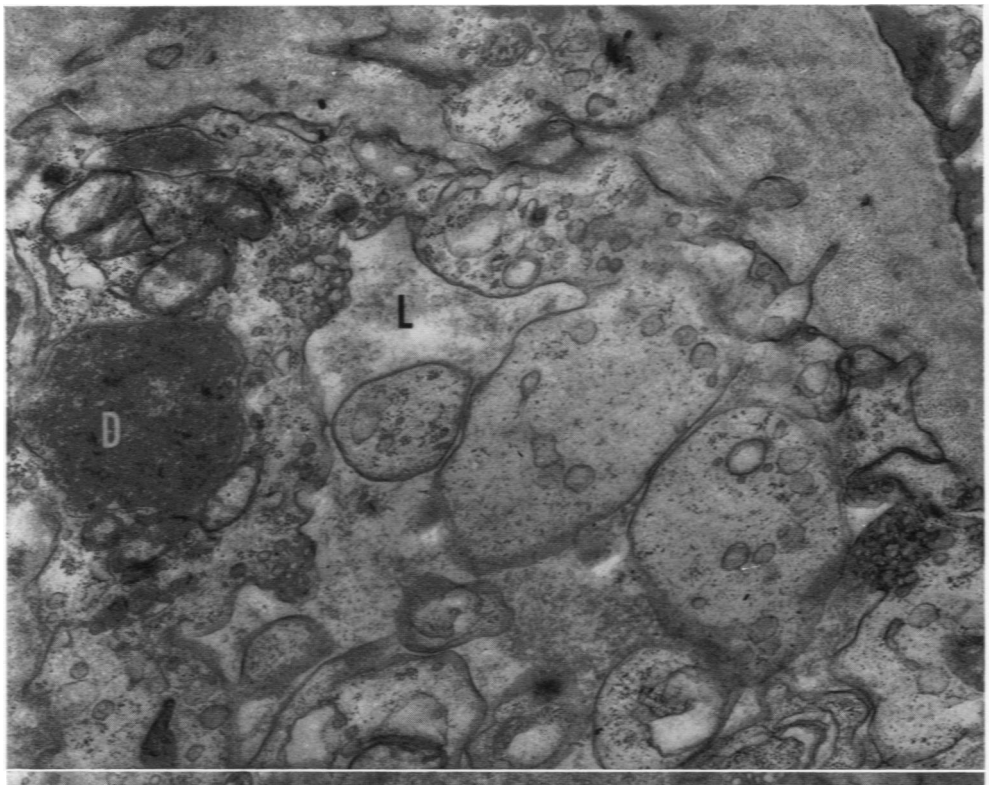
Fig. 2. Portion of glomerular capillary from patient with severe preeclampsia. Portions of endothelial cells narrow its lumen *(L)*. Cytofolds and pinocytic vesicles are evident. There is invagination of granular material *(D)* into endothelial cell cytoplasm. Plasma membrane of the latter still appears intact about the deposit. × 22,000.

Fig. 3. Portion of glomerulus from patient with severe preeclampsia. Mesangial zone is thickened by increase in lamina densa-like material and cells. × 14,000.



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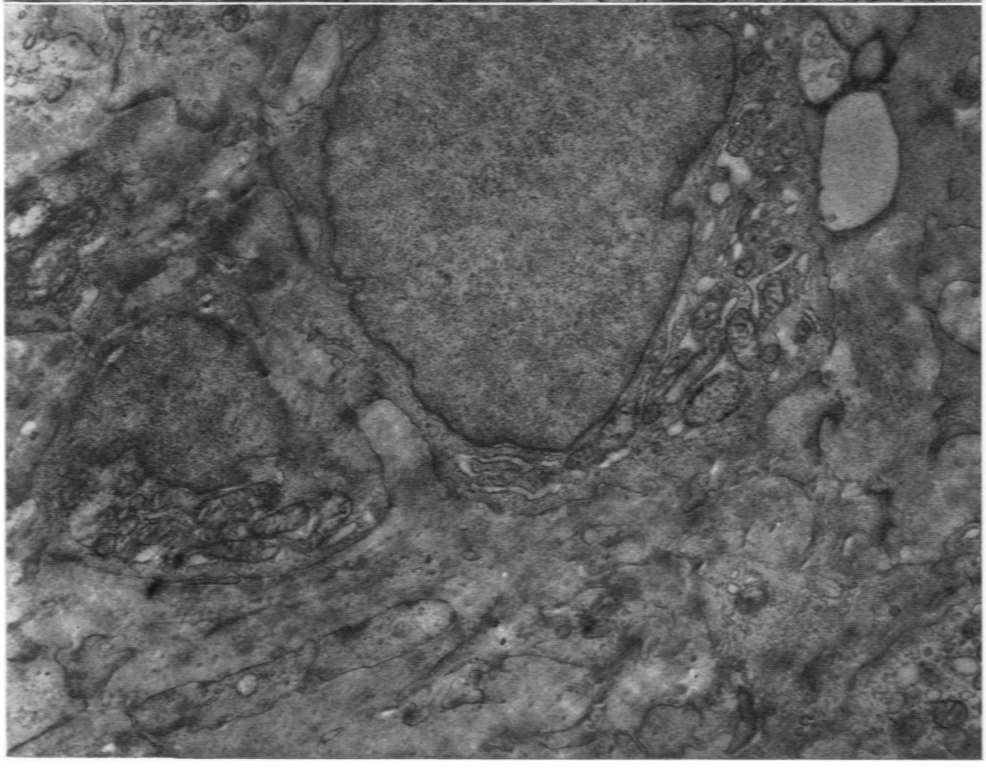

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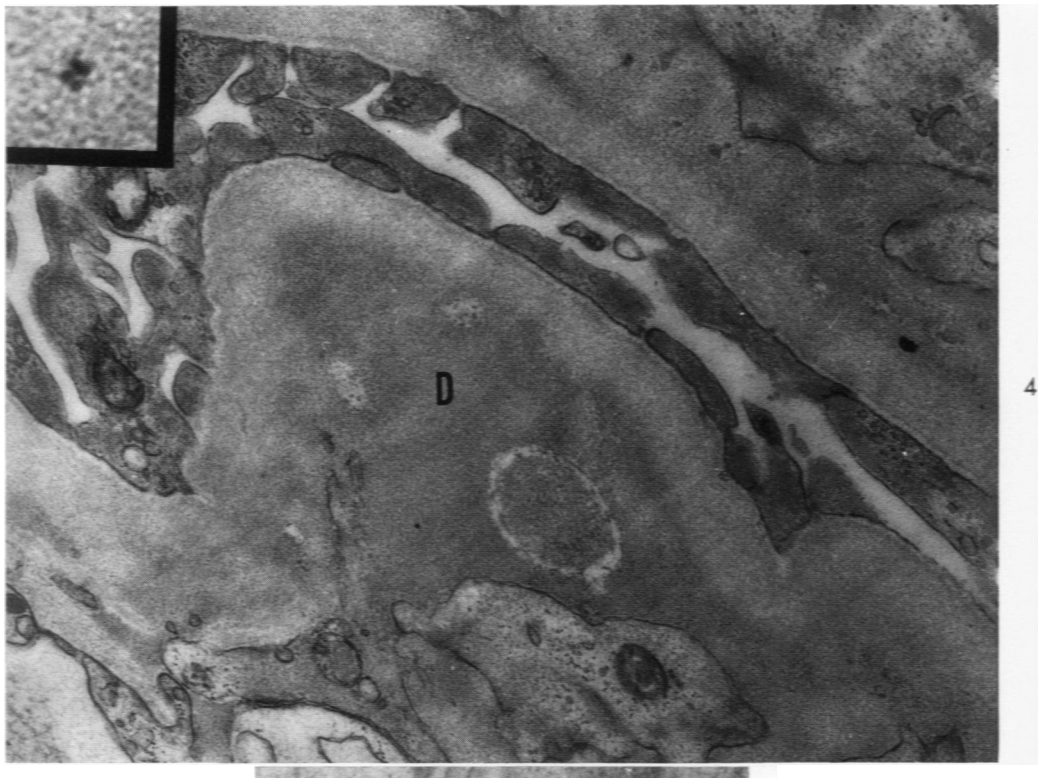
Fig. 4. Granular material comprising deposit *(D)* is present at endothelial aspect of lamina densa in glomerular capillary from patient with severe preeclampsia. × 22,500. **Insert** reveals granular nature of deposit. Tetrads of ferritin are also present. × 445,000.

Fig. 5. Large rounded electron-dense bodies occasionally noted in lamina densa of glomerular capillary from patient with preeclampsia. × 35,000.



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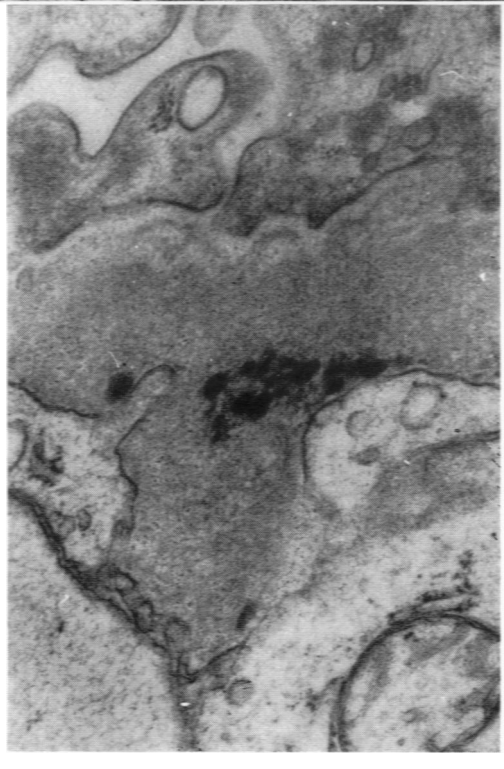

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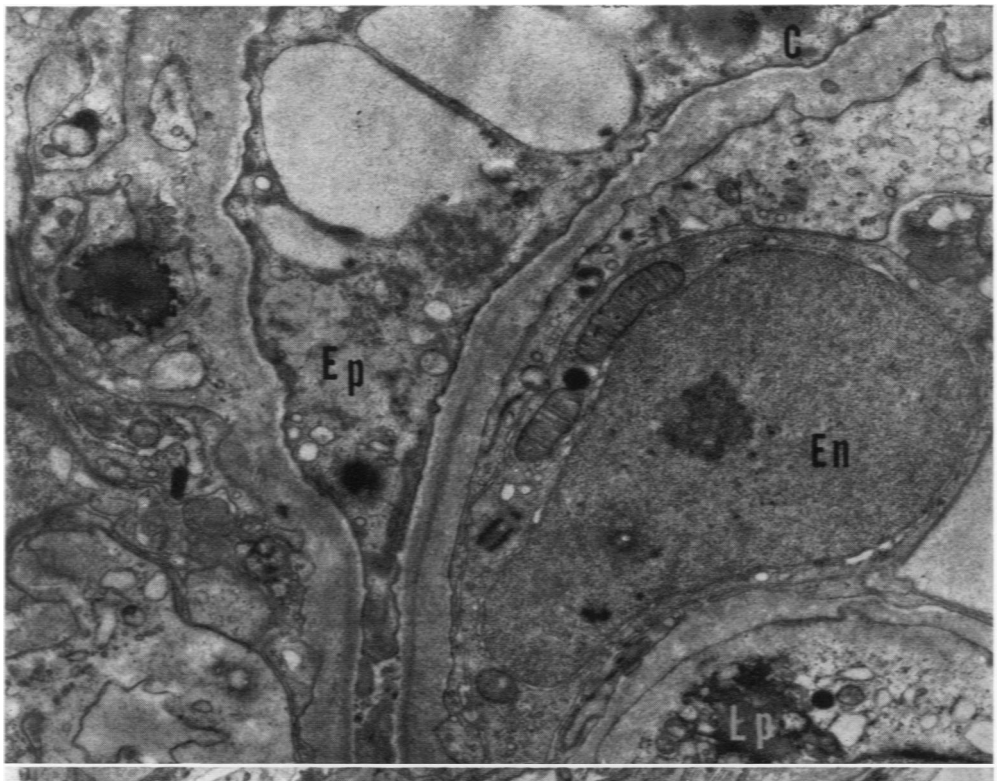
Fig. 6. Portion of glomerulus from patient with severe preeclampsia. Endothelial cells *(En)* are large and fenestrae are not evident. A lipid droplet *(Lp)* is noted in cytoplasm of one cell, and a centriole is seen in another. Epithelial cell *(Ep)* is vacuolated and its foot processes obliterated. Cytosomes *(C)* are noted in epithelial cytoplasm. Linear density within lamina densa, a very rare finding, is also demonstrated. × 11,750.

Fig. 7. Portion of glomerulus from patient considered to have essential hypertension. Focal endotheliosis is evident. × 3800.



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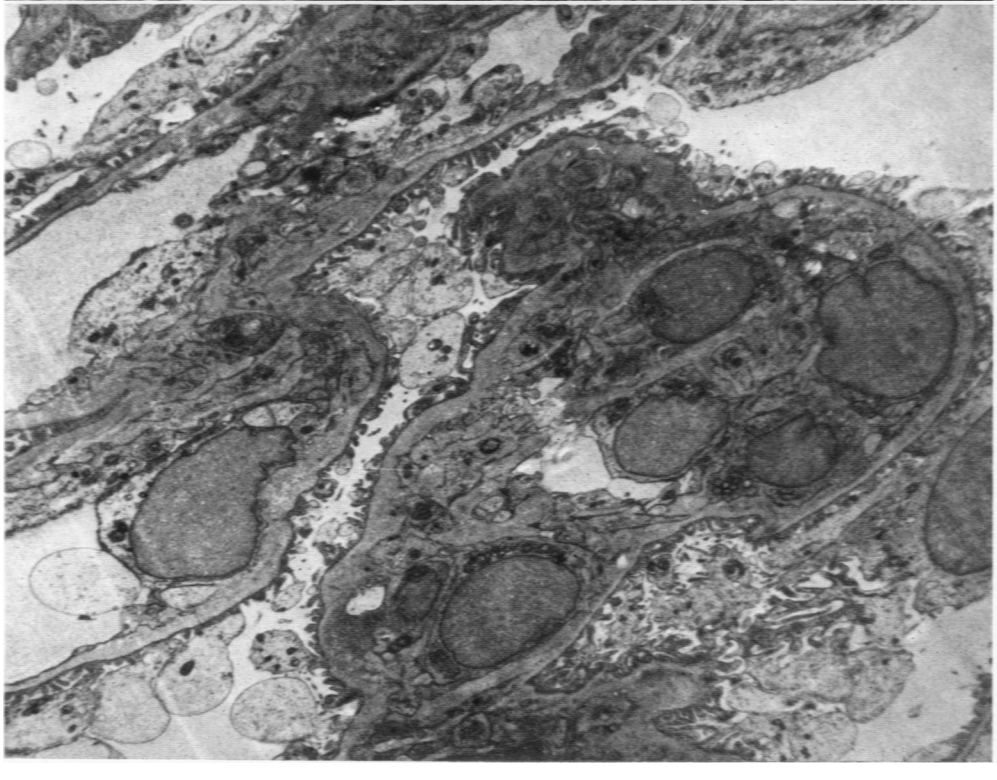

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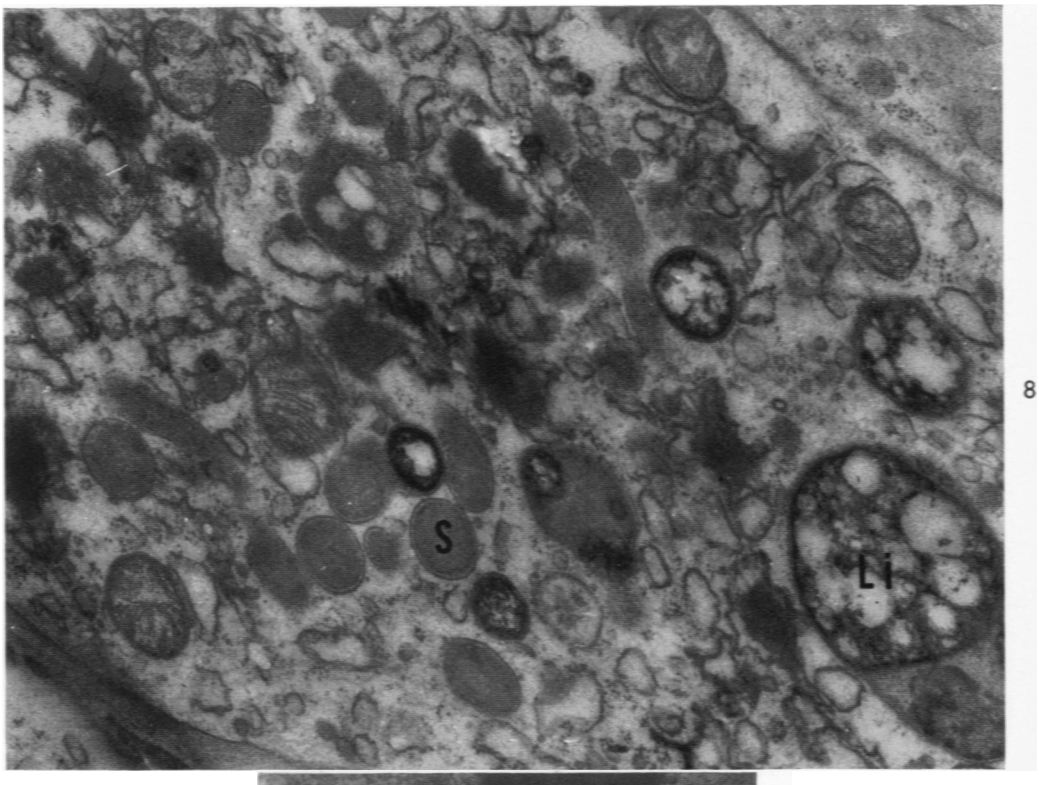
Fig. 8. Portion of juxtaglomerular cell from patient with essential hypertension and superimposed preeclampsia. The cytoplasm is replete with true secretory granules (*S*), as well as some forms appearing as lipofuscin (*Li*). × 25,000.

Fig. 9. Portion of juxtaglomerular cell from patient with severe preeclampsia. Round, as well as paracrystalline, forms of secretory granules are evident. The latter appear in Golgi lacunas. × 37,000.



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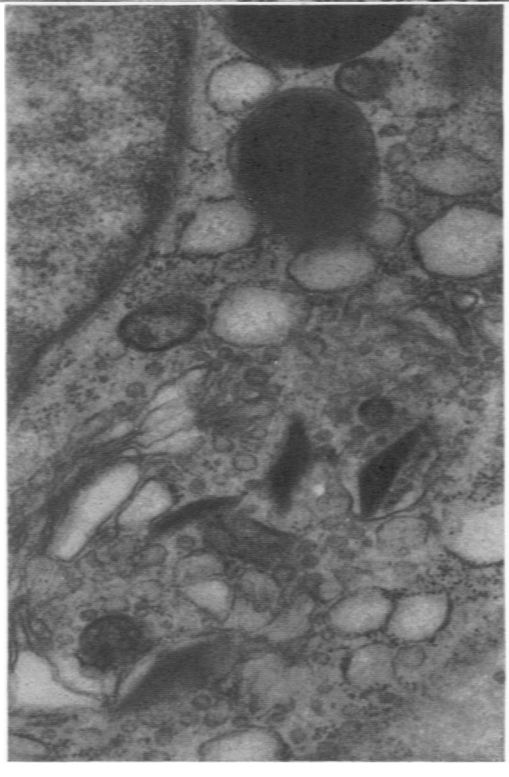

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